# Viability of customized, marked syringes for gentamicin delivery for the outpatient treatment of neonatal sepsis

## Considering demand and supply factors

### CONTEXT

Recently released World Health Organization (WHO) guidelines for managing a possible serious bacterial infection in young infants when referral is not feasible recommend using intramuscular (IM) gentamicin (in conjunction with oral amoxicillin) once daily for two or seven days (depending on the regimen) in the outpatient setting.[1] Countries that adopt these guidelines will need to consider the commodities needed to aid in their implementation at lower levels of care. One solution to simplify IM administration of gentamicin is a syringe with custom dose markings. [2] The aim of this brief is to inform on the viability of such a solution.

### TECHNICAL CONSIDERATIONS

Depending on the weight of the infant, the total dose of gentamicin recommended by WHO ranges between 8 mg and 24 mg.

Currently, the two most commonly available presentations of gentamicin are 40 mg/mL (in a 2-mL ampoule) and 10 mg/mL (in a 2-mL ampoule). For these two presentations, Table 1 displays the amount to be drawn into a syringe per weight band.

**Table 1. WHO weight bands and gentamicin doses.**

| WHO weight band (kg) | Gent IM daily dose (mg) | Gent 40 mg/mL in 2-mL amp (mL) | Gent 10 mg/mL in 2-mL amp (mL) |
|---|---|---|---|
| **1.5–2.4** | 8 | 0.2 | 0.8 |
| **2.5–3.9** | 16 | 0.4 | 1.6 |
| **4.0–5.9** | 24 | 0.6 | 2.4 |

Abbreviations: amp, ampoule; gent, gentamicin; WHO, World Health Organization.

Per available nursing manuals,[3,4,5,6,] the maximum volume to be administered intramuscularly at once in a neonate is from 0.5 mL to 1 mL; therefore, use of the 10 mg/mL (in a 2-mL ampoule) presentation would either require an injection volume that exceeds these recommendations or multiple injections of partial dose volumes for the two higher weight bands.

Due to the calculations needed to determine the dose volume by weight of the infant, health workers at the primary-care level may have difficulty accurately determining the correct amount of drug they should administer. Furthermore, they may have difficulty drawing up the appropriate dose volume using the measurement scale on the available syringe. For instance, the standard markings on larger syringes may decrease dosing accuracy, as shown in Figure 1 below.

[1] World Health Organization (WHO). *Managing Possible Serious Bacterial Infection in Young Infants When Referral is Not Feasible*. Geneva: WHO; 2015. Available at: http://www.who.int/maternal_child_adolescent/documents/bacterial-infection-infants/en/..

[2] PATH. *Gentamicin for Treatment of Neonatal Sepsis—A Landscape of Formulation, Packaging and Delivery Alternatives*. Seattle: PATH; 2015. Available at: http://www.path.org/publications/detail.php?i=2598.

[3] Government of Western Australia Department of Health. *Intramuscular Administration to the Neonate*. 2016. Available at : http://www.kemh.health.wa.gov.au/development/manuals/O&G_guidelines/sectionb/10/b10.4.1.pdf

[4] State of Victoria. *Neonatal eHandbook*. 2015. Available at: http://www.health.vic.gov.au/neonatalhandbook/procedures/intramuscular-injections.Shtm.

[5] Cohen MR. *Medication Errors*. American Pharmacist Association; 2007.

[6] James SR, Nelson K, Ashwill J. Medication Administration and Safety for Infants and Children. *Nursing Care of Children: Principles and Practice*. Elsevier Health Sciences; 2014: 307-316.

Figure 1: Syringes of different volumes with standard markings. Syringe sizes from left to right: 1mL, 3 mL, 5 mL, 10 mL, 1 cc. Photo credit: PATH/ Chelsea Schiller

Countries currently implementing the WHO guidelines (such as India and Bangladesh) are providing gentamicin at the health-post level using 1-mL syringes and/or insulin syringes to administer 40 mg/mL gentamicin.

## CONCEPT OF CUSTOMIZED SYRINGES

The concept of providing syringes with custom dose markings for the specified neonatal doses of gentamicin (corresponding to the three WHO weight bands) was identified as a potential solution to reduce the risks of both drawing an improper dose and repurposing the syringes for injection of other medications.[7] This approach would not require any repackaging or relicensing of the drug product. Currently, several human and veterinary medications are co-packaged with delivery devices with custom-marked dose volumes, as shown in Figure 2 below.


Figure 2: Custom-printed oral syringes marketed for dosing with infant Advil® (marked with doses in mL for treatment of infants of different weights) and veterinary Loxicom® (marked with image denoting species and dose volumes per the animal's weight in kg). Photo credit: Pfizer, Norbrook Laboratories

[7] PATH. *Gentamicin for Treatment of Neonatal Sepsis—A Landscape of Formulation, Packaging and Delivery Alternatives*. Seattle: PATH; 2015. Available at: http://www.path.org/publications/detail.php?i=2598.

## APPLICABLE ISO REQUIREMENTS FOR SYRINGE MARKINGS

The International Organization for Standardization (ISO) sets international standards for products to ensure quality, safety and efficiency. ISO Standard 7886 specifies requirements (including graduated scale, packaging, and labeling) for sterile, single-use, hypodermic syringes made of plastic materials[8] and intended for the aspiration of fluids or for the injection of fluids immediately after filling. In order for the customized syringe to comply, clause 10.1.1 states, "The syringe shall have either only one scale or more than one identical scales, which shall be graduated at least at the intervals given [in ISO 7886 specifications]. [Note 4: This requirement does not preclude the provision of additional graduation marks within the scale or as additions to the scale]." In terms of numbering, clause 10.2.2 states "The graduation lines shall be numbered at the volume increments given in table 1." Thus, for a 1-mL syringe, the increment between graduation lines to be numbered is 0.1 mL and the scale interval is 0.05 mL.

## MANUFACTURING CONSIDERATIONS FOR CUSOMIZED SYRINGES

Based on a literature review, the syringe specifications shown in Table 2 are optimal for IM delivery of gentamicin in neonates. Syringes that meet these specifications are currently available from WHO-prequalified syringe manufacturers, such as Wuxi Yushou Medical Appliances Co., Ltd. (Wuxi City, China) –also shown in Table 2.

**Table 2. Syringe specifications for neonatal IM administration.**

| | Optimal range | Yushou |
|---|---|---|
| **Gauge** | 22–25 G | 25 G |
| **Needle length** | 16–25 mm | 20 mm |
| **Gradations** | < 0.1 mL | 0.05 mL |
| **Volume** | ≥ 1 mL | 1 mL |

We contacted six companies to gauge feasibility and interest in manufacturing a customized syringe. Both the Wuxi Yushou company and Hindustan Syringes & Medical Supplies, Ltd. (HMD) (Ballabgarh, India) responded with quotations. The Wuxi Yushou company stated that three to five customized markings on a syringe could be done free of charge with orders of 100,000 syringes or higher. Their quotations are noted in Table 3.

**Table 3: Free on board[9] Shanghai prices.**

| Quantity | Price ($US/piece) |
|---|---|
| **100,000** | $0.045 |
| **1,000,000** | $0.038 |

[8] Excludes syringes for use with insulin.
[9] Free on board price quoted includes all charges up to placing the goods on board at Shanghai.

HMD quoted slightly higher prices for providing customized markings (compared to their existing product) as well as a one-time charge of US$1,000.00 for the development/printing of the revised markings on the barrel of their 1-mL Kojak auto-disable syringes with fixed needles. A minimum order quantity was required of 500,000 pieces ± 10%. Ex-works quotations are noted in Table 4.

**Table 4: Ex-works* prices**

| Quantity | Price ($US/piece) |
|---|---|
| **500,000** | $0.049 |

*Ex-works: price quotes includes charges only up to the seller's factory or premises.

For reference, the average price of a WHO prequalified syringe is US$0.04, and the 2-mL RUP syringe listed in the United Nations Children's Fund (UNICEF) supply catalogue is US$0.05 per piece. Our inquiries with syringe manufacturers confirmed that customized markings are technically feasible with little to no added costs.

## SUPPLY AND DEMAND CONSIDERATIONS FOR CUSTOMIZED SYRINGES

In order to better understand relevant factors for purchasing, distributing, and using a customized syringe, the project team considered recent feedback for another customized product concept from UNICEF as well as feedback on this concept from global health procurement specialists and the head neonatologist at a regional referral hospital in Uganda. Although the concept of a customized syringe for use in the outpatient treatment of neonatal sepsis may be appreciated by in-country program managers for its ability to improve the ease of administration of gentamicin in these settings, we identified the following complexities in introducing and maintaining use of a custom, single-purpose-only syringe.

**Training:** Introducing a customized syringe would result in the need for specific training in addition to training on the use of other available syringes in country.

**Logistics of pairing with gentamicin presentation:** Customized markings corresponding to WHO weight bands would need to be paired with the specific concentration of gentamicin suitable for those weight bands. Such syringes would only be used for this indication and would require that the precise concentration of gentamicin always be available. In a parallel example, UNICEF decided against customizing packaging of amoxicillin, which would have made it specific for treatment of child pneumonia, because amoxicillin is used for several other indications (including neonatal sepsis). Customizing packaging would have added implementation challenges.

**Procurement/distribution management:** The customized syringes would be a comparatively low-volume stock-keeping unit compared to other procured syringes, and would be an additional item to track and manage within the system. Stakeholders stated that even regular syringes are sometimes out of stock, so they worry that a very specific, single-purpose syringe could potentially be out of stock more frequently.

## CONCLUSIONS AND RECOMMENDATIONS

From a manufacturing standpoint, custom-marked syringes for IM administration of gentamicin in neonates are technically and financially feasible. However, the following needs to be considered:

- Complexities exist in introducing and maintaining use of a custom, single-purpose-only syringe, including training implications, logistics of pairing with gentamicin, and procurement/ distribution management of a comparatively low-volume stock-keeping unit compared to other available syringes.
- A custom-marked syringe would be best as a 1-mL syringe with 0.2 increment markings most relevant for gentamicin administration, so it may be that a regularly marked 1-mL syringe can be used effectively by health care workers for this purpose.
- Customized markings will not reduce the calculations associated with administration of gentamicin (given both the potential availability of different presentations of gentamicin and the ISO marking requirements).

**For the implementation of outpatient treatment of neonatal sepsis, pursuing wider availability of 1-mL syringes may be a better option than adding a single-purpose, customized syringe.**

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